Clinical Pharmacology Review of BLA 97-1251

Date: May 8, 1998

Reviewer: Carol Braun Trapnell, M.D.

Sponsor: Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

Product: SDZ CHI 621 (basiliximab, Simulect™) is a chimeric CD 25 monoclonal antibody of the IgG_1 isotype for intravenous injection

Product Class: Recombinant humanized IgG1 anti-Tac monoclonal antibody that acts as an antagonist at the interleukin-2 (IL-2) binding site of the p55 subunit (α chain, Tac antigen) of the high affinity IL-2 receptor (IL-2R or CD 25) on the surface of activated T-lymphocytes.

Proposed Indication: Prophylaxis of acute organ rejection in patients receiving renal transplants. Basiliximab will be administered concomitantly with an immunosuppressive regimen, including cyclosporine and corticosteroids

Proposed "Clinical Pharmacology" and "Precautions" section statement on drug-drug interactions in the Sponsor's Draft Labeling

CLINICAL PHARMACOLOGY

General

Simulect™ is a chimeric (murine/human) monoclonal antibody selectively targeted against IL-2Rα, which is expressed on the surface of activated T-lymphocytes in response to antigenic challenge. This specific binding of Simulect™ to IL-2Rα competitively inhibits the subsequent binding of interleukin-2, which signals T-cell proliferation.

Antibody Responses Of 270 (246 renal; 24 liver) patients treated with Simulect™ and tested for anti-idiotype antibodies, only one developed an anti-idiotype antibody response. Of 172 renal transplantation patients treated with Simulect™ in one clinical study, the incidence of human anti-murine antibody (HAMA) was 3.5% (6/172); since 4 of the 6 patients positive for HAMA also received OKT3, the incidence may be as low as 1.2% (2/172)

Pharmacokinetics

Complete and consistent blocking of IL-2Rα is maintained as long as serum Simulect™ levels exceed 0,2 µg/ml (by ELISA). As concentrations fall below this level, expression of IL-2Rα returns to pre-therapy values within 1-2 weeks. In vitro studies using human tissues indicate that Simulect™ binds only to lymphocytes and macrophages/monocytes.

De Novo Renal Transplantation (Adults)
Single-dose and multiple-dose pharmacokinetic studies have been conducted in patients undergoing kidney transplantation. Cumulative doses ranged from 15 mg up to 150 mg.

Peak serum concentrations following intravenous infusion of 20 mg over 30 minutes is 7.1 ± 5.1 mg/L. There is a dose-proportional increase in C_{max} and AUC up to the highest tested single dose of 60 mg.

The volume of distribution at stead state is 8.6 ± 4.1 L. The extent and degree of distribution to various body compartments have not been fully studied.

The terminal half-life is 7.2 ± 3.2 days. Total body clearance is 41 ± 10 ml/h.

No clinically relevant influence of body weight or gender on distribution volume or clearance has been observed in adult patients. Elimination half-life was not influenced by age (20-69 years), gender or race. The median duration of IL-2Rα suppression was 35 days (range 23-45 days). (See DOSAGE and ADMINISTRATION)

De Novo Renal Transplantation (Pediatric)
In one clinical study in 8 pediatric de novo renal transplantation patients 2-12 years of age (up to 37 kg) the central distribution volume was 1.7 ± 0.6 L, half-life was 9.4 ± 4.9 days and clearance was 20 ± 4 ml/h. Clearance and volume were not influenced by age (2-12 years), body weight (9-37 kg) or body surface area (0.44-1.20 m^2). The disposition of Simulect™ in pediatric renal transplantation patients was characterized by an average 50% lower clearance compare to adult patients, whereas the relationship between serum concentration and receptor saturation was similar in both age groups. (See DOSAGE and ADMINISTRATION)

De Novo Liver Transplantation (Adults)
A multiple-dose pharmacokinetic study has been conducted in 23 patients undergoing liver transplantation. Simulect™ was administered as either a bolus injection or infusion with the first dose administered within 6 hours after reperfusion of the graft. The total dose administered was 40 mg (4 x 10 mg or 2 x 20 mg). No difference in exposure (AUC) was observed between the two dosage regimens. Disposition in adult liver transplantation patients is characterized by a steady-state distribution volume of 7.5 ± 2.5 L, half-life of 4.1 ± 2.1 days, and clearance of 75 ± 24 ml/h. Contributing to clearance were drug loss via drained ascites fluid and post-operative bleeding. Offsetting the faster drug clearance was a slower receptor-saturating concentration threshold of 0.1 µg/ml in this population. Hence, the duration of IL-2Rα blockade at a given Simulect™ dose level is similar to that seen in adult renal transplantation patients.

PRECAUTIONS

Drug Interactions
Because Simulect™ is an immunoglobulin, no metabolic interactions are to be expected. Therefore, no formal drug-drug interaction studies have been conducted.

Clinical Studies Submitted in Support of the Above Labeling

The sponsor has submitted data obtained from 7 studies in support of the labeling noted above. These are summarized in the following table.

Study	Population	Sampling Frequency	Evaluable for PK	Total Dose (mg)
CHIB101	Adult, Renal	Intensive	24	15-150
CHIB105	Adult, Renal	Intensive	15	20-60
CHIB106	Adult, Renal	Intensive	28	40-60
CHIB152	Pediatric, Renal	Intensive	8	5-15
CHIB201	Adult, Renal	Limited	39	40
CHIB352	Adult, Renal	Limited	164	40
CHIC101	Adult, Liver	Intensive	23	40

It should be noted that the sponsor's human pharmacokinetic summary document was adequate in the descriptions of the clinical pharmacokinetic properties of basiliximab, and will be attached to this review to provide the full details of the analyses and the studies. The reviewer has no substantive objectives to any of the analyses that were performed for the adult studies, thus, this review will briefly discuss each study with the details described by the attached sponsor's summary

Bioanalytical Methods

Clinical studies CHIB101 and CHIB105 employed a [redacted] to assess the concentrations of basiliximab from serum samples. This assay, which measured serum basiliximab concentrations by a competition assay between "cold" and radiolabelled basiliximab, had a lower limit of detection of [redacted] and a corresponding upper limit of detection of [redacted] However, since samples were diluted [redacted] for this assay, the practical lower limit of quantitation was [redacted]. However, it was discovered that soluble IL-2Rα present in the serum samples led to significant assay interference. Subsequently, then, an [redacted] was developed which did not have this interference problem and was used to analyze approximately half of the pharmacokinetic samples from CHIB105 and all samples from the rest of the studies.

Reviewer's Comment

Only the data which were generated from the [redacted] analytic method will be considered for pharmacokinetic assessment of basiliximab. This is also what the sponsor chose to do as well.

The [redacted] assay was evaluated by comparing [redacted] basiliximab antibodies. A [redacted] antibody gave a binding capacity for basiliximab [redacted] times higher to that of the [redacted] antibody. The competition curve obtained with the polyclonal antibody was [redacted] times more sensitive to that of the [redacted] Thus, the [redacted] anti-basiliximab antibody was chosen to use for the [redacted] assay.

The [redacted] assay had a range of lower limit of detection of [redacted] and an upper limit of detection of [redacted] The within assay variability was [redacted] for the highest quality control sample and [redacted] for the lowest quality control sample. The between assay variability was [redacted], for all quality control samples. The assay accuracy was [redacted] for the highest quality control sample and [redacted], for the lowest quality control sample. The quantification limit corresponded to the lowest quality control sample: [redacted] After [redacted] cycles of freeze/thaw, a decrease of 10%, 18% and 14% were observed for the spiked samples tested.

CLINICAL PHARMACOLOGY STUDIES SUBMITTED TO SUPPORT LABELING CLAIMS

Adult Studies

The sponsor performed three, intensive, pharmacokinetic studies in adult renal transplantation patients which served to define the clinical pharmacology of basiliximab in this patient population. These studies, CHIB 101, 105 and 106, were intensive, pharmacokinetic, dose-ranging studies which were used to find the optimal dose to cause saturation of IL-2R receptors for 30 and 45 days. A fourth study, CHIB 201, the pivotal Phase 2/3 trial, contained a nested pharmacokinetic study on a subset of the patients in the trial. These studies will each be briefly described below.

Protocol CHIB101

Study CHIB101, entitled, "Safety and Tolerability of SDZ CHI 621 Given AS Prophylaxis for Acute Rejection in Kidney Transplant Patients", was a Phase 1, open label, dose escalation study of basiliximab in 24 male and female patients over the age of 18 years receiving their first, mismatched, cadaveric renal transplant at two transplant centers in the United Kingdom. Six cohorts of 4 patients each received escalating doses of basiliximab at doses of 2.5, 5, 10, 15 or 25 mg administered six times over a 24 day study period, with an additional four patients enrolled in the 10 mg dosing cohort. Total doses administered were 15, 30, 50, 80 and 150 mg, respectively. All doses were administered over as a 30 minutes IV infusion, with the first dose being given prior to transplantation, and the additional doses being administered on postoperative days 2, 6, 11, 17 and 24. All study patients received basiliximab in combination with either cyclosporine and methyprednisolone or cyclosporine, methylprednisolone and azathioprine, depending on the transplant center. Cyclosporine doses were modified according to assessments of cyclosporine trough levels obtained regularly during the study.

Blood was obtained on study days 0 and 2 (first and second basiliximab doses) just prior to basiliximab administration, then 0.5, 1, 2, 4 and 24 hours after the infusion, then at 24 hour intervals during the duration of hospitalization, at least twice weekly until study day 24, at least 3 samples were to be obtained between study days 24 and 31 and, finally, weekly through day 63 (week 9). Basiliximab concentrations were determined using the [redacted] described previously in this review.

Pharmacodynamic assessments were also made during this study using flow cytometry to measure the percent of peripheral T lymphocytes expressing the CD25A and CD25B antigens over time from serial venous blood samples. All paired basiliximab concentration and CD25A data were pooled to assess a concentration: effect relationship. Finally, blood was obtained during the study period for assessment of the formation.

This pharmacokinetic results of this study were confounded by the use of the —— analytic assay described above, resulting in significant assay interference from soluble IL-2R contained the samples. This was confounded these results and was recognized by the sponsor; two additional intensive studies were done using the improved, —— assay (CHIB105 and 106). It should be noted that there were no anti-idiotypic antibodies formed in any of the patients in this study. Further, there were no unexpected or untoward adverse effects.

Protocol CHIB105

Protocol CHIB105 entitled, "Safety and Tolerability of SDZ CHI 621 Given as Prophylaxis for Acute Rejection in Kidney Transplant Patients", was a Phase 1, open label, dose ranging study, prospective study of basiliximab over 12 weeks in adult male and female patients receiving their first, mismatched cadaveric renal transplantation at 2 transplantation centers in the United Kingdom and one center in Norway. The study objectives were to determine the pharmacokinetic characteristics of basiliximab after a single dose and after two doses by measuring basiliximab serum levels at regular intervals after each dose and to assess the effectiveness, safety, tolerability and immunogenicity of basiliximab in these patients.

Six different basiliximab dosage regimens were tested in 38 patients. These regimens and the number of patients studied are listed below:

Dosage Regimen	Patients Studied
20 mg on day 0	4
20 mg on day 0 and day 7	5
20 mg on day 0, day 4 and day 10	5
15 mg on day 0 and day 7	5
20 mg on day 0 and day 4	9
20 mg on day 0, day 2 and day 4	11

Blood was obtained for determination of basiliximab serum concentrations just prior to each dose, then 30 minutes and 2 hours after the completion of the infusion, daily for 14 days, then at weeks 4, 6, 8 and 12 of the study.

Pharmacokinetic Assessment

Serum concentrations of basiliximab were initially measured using the — assay methodology as described above. Further, at the completion of the study, basiliximab serum concentrations from 16 of the study subjects were determined using the previously described —— assay. Detailed pharmacokinetic evaluations were performed using the results from the —— assay; the concentration data from the — assay was only used to estimate the basiliximab terminal half-life.

The pharmacokinetic evaluations which were done included both noncompartmental as well as a compartmental analyses. The compartmental analysis determined C_{max}, AUC from time=0 to the last quantifiable drug concentration (AUC(0-t_z)) and $t_{½}$. The compartment analyses was done using an open, two-compartment model with first-order elimination from the central compartment by nonlinear regression. Measured concentrations were weighted as 1/conc. The relationship between cumulative AUC(0-t_z) and total dose was explored by weighted linear regression with weights equal to the inverse of dose. The relationship of cumulative AUC(0-t_z) to weight-adjusted dose (mg/kg) was explored by unweighted linear regression. Dose proportionality was not excluded if the overall regression was statistically significant and the 95% confidence interval for the intercept included zero.

The influence of body weight on basiliximab volume of distribution and clearance was explored by conventional linear regression analysis. Data was also weight-normalized to 70 kg and the distributions compared graphically by boxplots and by comparing the between-subject coefficients of variation.

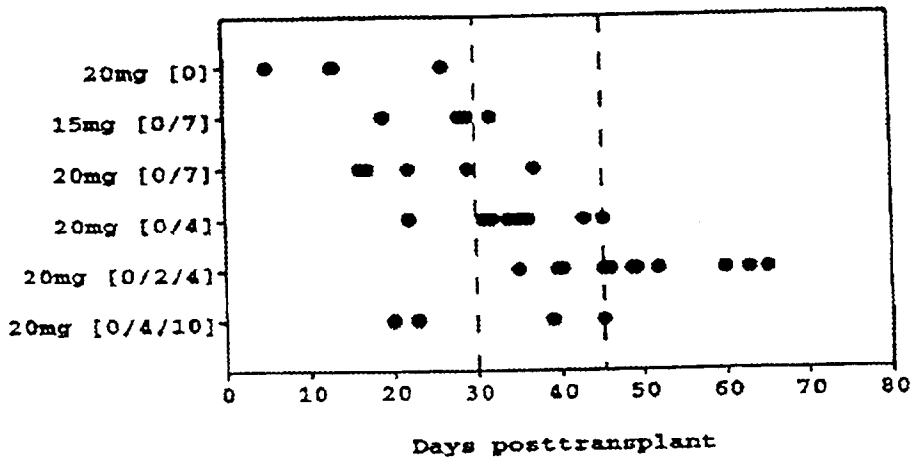
Pharmacodynamic evaluations included evaluation of lymphocyte subsets and T lymphocytes expressing selected activation antigens. The percent peripheral T lymphocytes expressing the CD52A and CD25B antigens over time from serial venous blood samples was compared to serum basiliximab concentrations for each subject. All paired —— concentration and CD25A data were pooled to produce a concentration-effect scatterplot to examine the relationship between drug concentration and immunosuppression. Finally, serum was analyzed for the presence of anti-idiotype antibody formation and response.

Results

39 study patients were recruited into this study; 38 underwent renal transplantation. The average age of the subjects was 48 years (range 18-71), 67% of the patients were men. Thirty-four of the patients were Caucasian, two were Black, two were Asian and one was Indian. The 6 dosing cohorts were comparable in respects to all evaluated demographic criteria. Concomitant medication include cyclosporine and steroids at one study site and cyclosporine, steroids and azathioprine at the other 2 sites. Cyclosporine trough levels were monitored at least two times per week and doses of this drug were adjusted accordingly.

Pharmacokinetic Results

The goal of this study was to determine the dosing regimen which would yield concentrations ≥ 0.2 µg/ml for a period of between 30-45 days. As is shown in the figure below, this goal was accomplished most successfully in the cohort which received basiliximab at doses of 20 mg on days 0 and 4. Evaluation of the individual patient concentration versus time data confirmed this finding.



The pharmacokinetic parameters derived from the samples analyzed using the —— assay were a Cmax following the first 20 minute basiliximab infusion of 7.1 ± 5.1 µg/ml. Cumulative AUC values rose in proportion to the total dose over the dose ranges studies, V_{ss} was 8.0 ± 6.2 L, the $t_{½}$ was 8.5 ± 4.5days and the Cl was 33 ± 22 ml/h. Neither the Cl or the V_{ss} was correlated to body weight. Further, weight-normalizing the pharmacokinetic parameters did not significantly change the between-subject variability for Cl or V_{ss}.

Protocol CHIB106

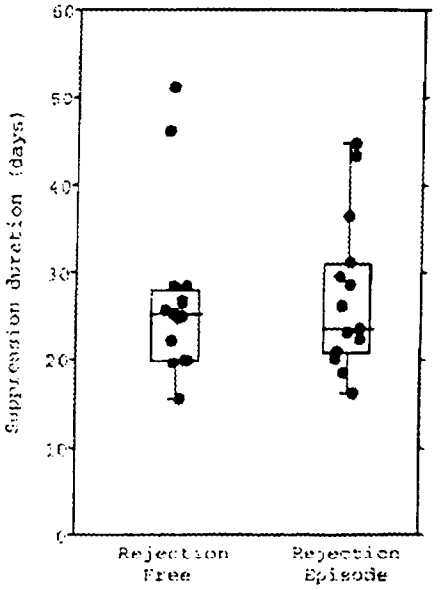
Study CHIB106 entitled, Safety, Tolerability and Pharmacokinetics of Three Doses of Basiliximab Given as Prophylaxis for Acute Rejection in Kidney Transplant Recipients", was a Phase 1/2 study in 32 patients who were the recipients of primary, mismatched cadaveric kidneys. The main objective of this study was to determine the single dosing regimen which would keep basiliximab concentrations > 0.2 µg/ml for a period of between 30 and 45 days. The study planned to evaluate the pharmacokinetics and pharmacodynamics of 40, 60 and 80 mg given as a single dose, but the 80 mg dose was never studied due to the degree of IL-2R receptor suppression seen with the 60 mg dose.

This study showed that the pharmacokinetics of basiliximab were consistent with the findings seen in Protocol CHIB105 as shown in the following table:

SUMMARY TABLE 1
Pharmacokinetic Parameters of Basiliximab
Following Single Intravenous Infusion of 40 or 80 mg
Mean ± SD (median)

Parameter	40 mg (n = 24)	80 mg (n = 6)
C_{max} [µg/ml]	9.32 ± 4.49 (8.66)	11.63 ± 4.24 (11.36)
C_{max}/Dose [µg/ml per mg]	0.23 ± 0.11 (0.21)	0.15 ± 0.07 (0.19)
AUC [µg·day/ml]	41.2 ± 16.7 (37.3)	72.3 ± 31.3 (66.4)
AUC/Dose [µg·day/ml per mg]	1.03 ± 0.42 (0.93)	1.21 ± 0.52 (1.11)
CL [ml/h]	48.2 ± 18.1 (44.8)	39.4 ± 14.7 (37.8)
V_z [L]	8.8 ± 3.2 (8.2)	7.5 ± 1.8 (7.5)
$t_{1/2}$ [days]	5.8 ± 2.0 (5.3)	6.0 ± 1.9 (5.7)

The relationship between the number of days of suppression and the number of rejection episodes seen 3 months after treatment is shown below:



Finally, there were no anti-idiotype antibodies detected in the study patients.

This study concluded that adequate basiliximab concentrations to suppress IL-2R receptors for 30-45 days were achieved with a single dose of 40 mg of basiliximab.

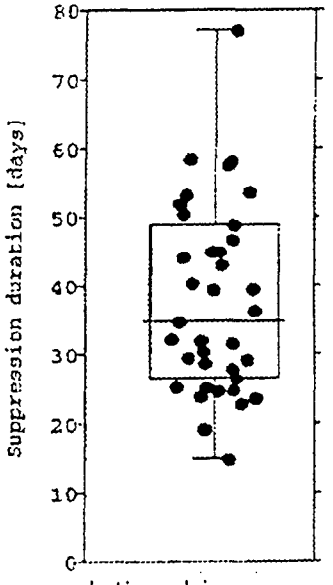
Protocol CHIB201

Study CHIB152 entitled, "A multicenter, double-blind, placebo-controlled trial of Simulect for Prevention of Acute Cellular Rejection in Renal Allograft Recipients", was a Phase 2/3 study to assess the effectiveness of safety of 40 mg basiliximab given as 20 mg doses on the day of and 4 days post transplantation to prevent renal allograft rejection. This regimen was selected to the results from the earlier pharmacokinetic studies showing that the majority of patients would have an estimated suppression duration of between 27-49 days, which was within the targeted duration of suppression of 30-45 days.

A nested pharmacokinetic study was carried out at 5 of the study centers, which evaluated the basiliximab pharmacokinetics in 40 basiliximab patients and 39 placebo patients. Blood was obtained prior to transplantation, and at scheduled clinic visits on study days 10, 21 and 28 post-transplant. Serum basiliximab were determined by the validated — assay described earlier in this review; log-linear regression was performed to derive the terminal elimination rate

constant for each patient. This was then used to calculate basiliximab $t_{½}$ as well as the duration of IL-2Rα-saturating concentrations present.

The demographics of the subpopulation of patients who participated in the pharmacokinetic substudy reflected the overall study demographics. The pharmacokinetic data from this trial was, again, in good agreement with the previous values obtained in the intensive, pharmacokinetic studies which had been performed. The duration of IL-2R saturation was, again, in good agreement with the results seen previously ,as shown in the following box plot:



Basiliximab exposure-to-efficacy relationships were assessed in an exploratory fashion, as the limited number of patients participating in the pharmacokinetic assessments prevented more rigorous analyses. A limited number of biopsy-confirmed acute rejection episodes occurred in the pharmacokinetic study subpopulation. Thus, it did not appear that the duration of receptor saturation in subjects experiencing a biopsy-confirmed acute rejection episode differed from subjects who remained rejection-free for the 6 month observation period. However, the overall study results support the addition of basiliximab to the immunosuppression regimen.

Pediatric Patients

The sponsor undertook a pharmacokinetic and safety study in pediatric de novo renal transplantation patients. This study was done in two parts. Part 1 enrolled 12 patients into a phase 1, pharmacokinetic study. Phase 1 results from 8 patients were submitted in the original BLA; an update which included 12

patients was included in the 120 day safety submission. The Phase 2 portion of this study is ongoing at the time of the review; no data has been submitted to date. Thus, this review will discuss only the Phase 1 pharmacokinetic information in the 12 patients who have participated in this portion of the trial.

PROTOCOL CHIB152

Title: A multicenter, open-label, pharmacokinetic/pharmacodynamic , safety and tolerability study of Simulect™ in pediatric *de novo* renal transplant recipients

Summary of Trial:

This is an ongoing Phase 1/2 study in pediatric de novo renal transplant recipients of a cadaveric or living-related donor kidney. The study was divided into two phases; the data submitted are from the first phase of the trial. In this phase, 12 patients were enrolled. Patients eligible for this study included both males and females under the age of 16 years receiving a primary cadaveric or living donor renal transplant and in whom renal biopsies were possible. Basiliximab was administered as an intravenous bolus injection in doses of 12 mg/m^2 on days 0 and 4. The largest dose which was to be administered was 20 mg. Background immunosuppression consisted of cyclosporine and steroids for 12 months; after day 28, azathioprine was permitted at centers where triple therapy was the standard treatment regimen. Blood samples were obtained for 12 weeks at baseline, just prior and 30 minutes after each basiliximab injection and on days 1. 2, 3, 5, 6, 7, 14, 21, 28, 35, 42, 56, 70, and 84 following transplantation to determine serum basiliximab concentrations via an assay that was described earlier this review. At one center, blood was obtained for flow cytometric analysis of peripheral T lymphocytes expressing IL-Rα (CD25). Other data that was obtained include information on effectiveness and safety of basiliximab in these children. Data for 12 weeks of follow-up was included in this report.

Study Results

Demographics

The study enrolled 12 children into two age cohorts. Cohort 1 consisted of 6 patients < 9 years old and Cohort 2 consisted of 6 children ≥ 9 and < 16 years of age. Demographic information for these two cohorts is noted in the following table:

	Cohort 1	Cohort 2	Total
Age (years) mean±SD (range)	4.2 ± 3 (2-8)	12.3±1.4 (11-14)	8.3±4.8 (2-14)
Sex (M/F)	3/3	5/1	8/4
Race (C/B/A/O)	3/1/1/1	5/1/0/0	8/2/1/1
Weight (kg) mean±SD (range)	15.2±6.3 (9.1 - 23.6)	36.9±5.2 (29.6-44.2)	26.0±12.6 (9.1-44.2)

There were 3 cadaveric and 3 living donors for Cohort 1 and 4 cadaveric and 2 living donors for Cohort 2. The mean cold ischemic time was similar for both groups, 26.5 hours in Cohort 1 and 24.2 hours in Cohort 2.

All 12 patients received both doses of basiliximab on days 0 and 4 at a doses of 12 mg/m^2.

Pharmacokinetic Results

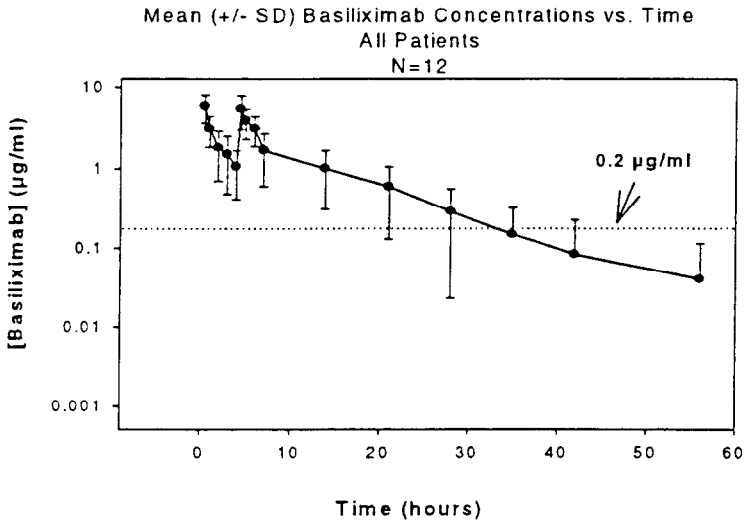
The pharmacokinetic parameters determined from the basiliximab serum concentration data were separated to two pediatric age subgroups (<12 years and ages 12-16) based on FDA's pediatric rule. These data were compared to basiliximab pharmacokinetic data from adult patients. The following table compared these three groups:

Parameter	Children Ages 2-11	Adolescents Ages 12-16	Adults
C_{max} (µg/ml)	6.6 ± 2.1	4.4 ± 1.9	4.7 ± 2.2
AUC (µg•day/ml)	47.1 ± 18.1	34.7 ± 19.3	41.2 ± 16.7
Cl (ml/h)	17.1 ± 5.6	45.3 ± 24.7	44.9 ± 15.8
Vc (L)	1.6 ± 0.8	4.2 ± 2.3	4.9 ± 1.5
Vss (L)	5.2 ± 2.8	10.1 ± 7.6	8.9 ± 2.5
$t_{½}$ (days)	11.5 ± 6.3	7.2 ± 3.6	5.8 ± 2.0

These data show that, with the *a priori* down-scaling of the dose based on body surface area, the cumulative AUC in children and adolescents was similar to that in adults. Total body clearance In children was decreased by about 50% compared to adolescents and adults. Peak concentrations were higher in children than in adolescents and adults, probably due to the differences in

central and steady-state volumes of distribution in children because of their smaller size.

Pharmacodynamic results indicate that that all 12 pediatric patients had basiliximab concentrations greater than the targeted minimum of 0.2 µg/ml with for an average of 31 ± 12 days (range of 20 - 63 days), which was similar to the duration seen in adult patients. Below are the pediatric mean ± SD basiliximab concentrations versus time which shows this very nicely:



Conclusions

The sponsor concluded that these pharmacokinetic and pharmacodynamic data show that basiliximab clearance in children < 12 years of age is approximately half that of adolescents and adults. Further, drug disposition in adolescents is similar to that of adults. The sponsor used these data to recommend a change in the basiliximab dose to a fixed dose regimen based on body weight being greater or less that 40 kg. The pediatric dosing recommendations in the draft label submitted by the sponsor are as follows:

> "In pediatric patients weighing less than 40 mg, the recommended total dose in 20 mg, given in two doses of 10 mg each. In pediatric patients weighing 40 kg or more, the recommended dose is the adult dose, i.e., a total dose of 40 mg, given in two doses of 20 mg each. The first dose should be given within 2 hours prior to transplantation surgery. The second dose should be given 4 days after transplantation."

This conclusion is problematic for a number of reasons. First, the patients in the pediatric trial who were 2 years of age received a total dose of 10 mg, given as two 5 mg doses. These doses kept the mean basiliximab serum concentration ≥ 0.2 µg/ml to day 35 after dosing. Recommending that these patients receive 10 mg per dose (as would be the case since their weight would be < 40 kg), would result in twice the basiliximab concentrations which would likely extend the period of IL-2Rα suppression out beyond 45 days and result in a greater degree of immunosuppression. Further, fixing the basiliximab dose based on this weight cut0off could result in a child below the age of 12 who might weigh > 40 kg receiving 20 mg on days 0 and 4 but the predicted, age-related, slower basiliximab clearance would also prolong the period of immunosuppression.

In sum, the sponsor should be asked to change the pediatric dosing section of the label to recommend dosing on a mg/M2 basis as was done in this trial. If data from the ongoing second of this study, which will be based on fixed doses of basiliximab, demonstrate basiliximab to be safe and efficacious uses these regimens, then the basiliximab dosing recommendations may be modified.

OVERALL CONCLUSIONS FROM THE CLINICAL PHARMACOLOGY REVIEW

1. The clinical pharmacology program which the sponsor undertook to describe the pharmacokinetics and pharmacodynamics of basiliximab in the prevention of renal allograft rejection in adult transplant patients generated data of good quality with sound conclusions. Analyses were done showing no changes in basiliximab's pharmacokinetic based on weight, race or gender.

2. It is reasonable to suspect that the likelihood of pharmacokinetic interactions between basiliximab and other drugs used in this patient population is minimal, thus the decision by the sponsor not to undertake any formal drug interactions studies is acceptable.

3. The pediatric dosing section of the label should be modified to reflect dosing recommendations based on body surface area as was done in the Phase 1 study in this population. Further modification of these recommendations to fixed doses of basiliximab based on weight may be considered when data to support such recommendations are submitted to the Agency.

4. It does not appear that basiliximab induces the formation of anti-idiotype antibodies to the compound based on the data presented on the data in these clinical pharmacology studies.

5. All references to basiliximab pharmacokinetics and suggestions on dosing basiliximab in patients receiving liver transplantation should be removed from the labeling. These data can be added to the label if the sponsor subsequently submits data to support a clinical indication for this patient population.

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